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SKELETAL UPTAKE OF (99M) TC DIPHOSPHONATE IN RELATION TO LOCAL --ETC(U)
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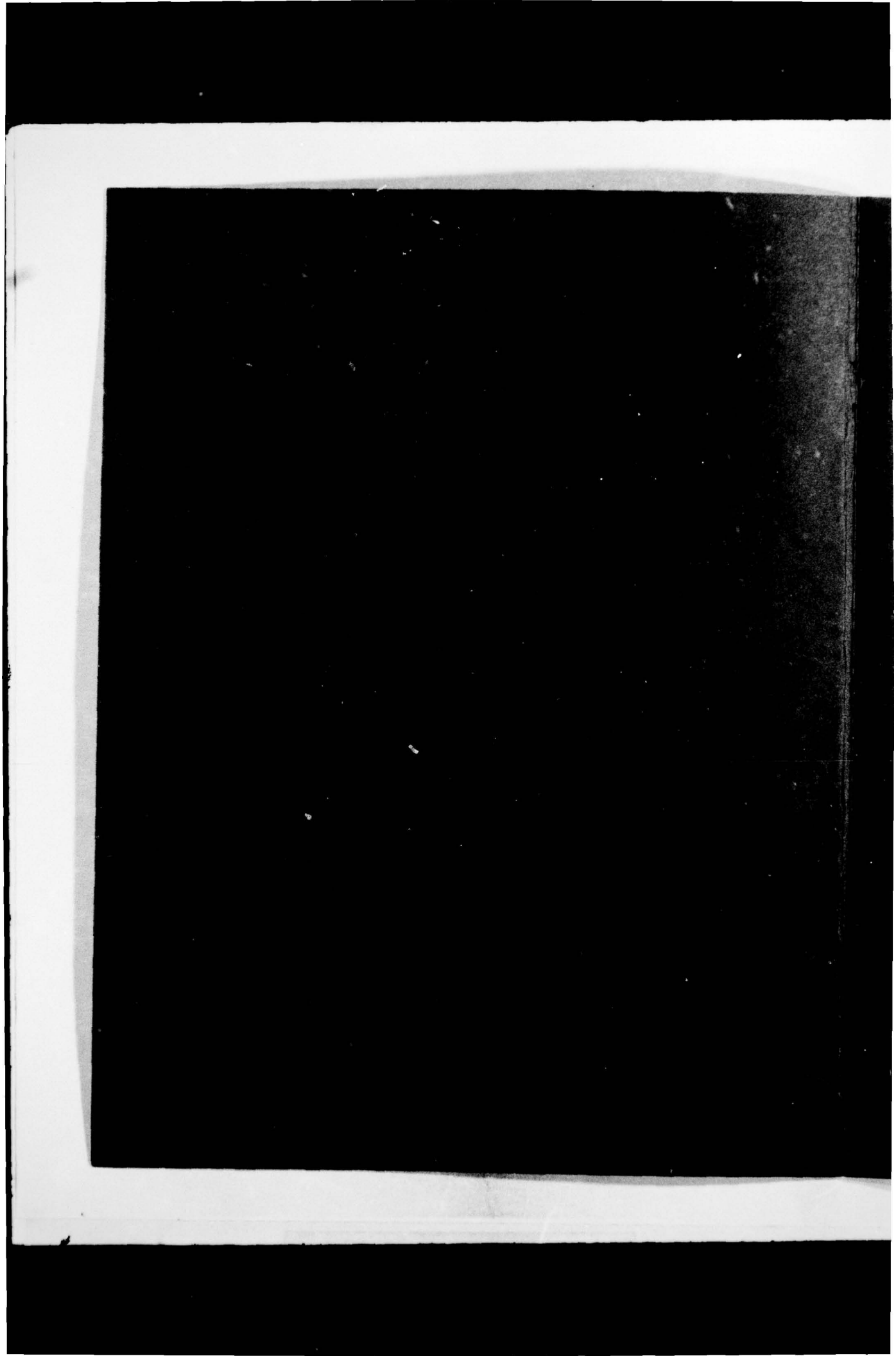

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The right-left (R-L) ratios for tibial uptake of ^{99m}Tc diphosphonate (EHDP) and relative blood flow (from microsphere distribution) were determined in control rats and rats with right femoral artery ligation or healing right tibial fractures. There was highly significant correlation ($r = 0.917$; $P < 0.0001$) between the ^{99m}Tc EHDP uptake and relative blood flow for relative flow ratios < 1.7. When relative

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tibial blood flow was >1.7, there was little further increase in ^{99m}Tc EHDP uptake. In addition, femoral artery ligation in rats with healing fractures resulted in a more marked reduction of flow than of ^{99m}Tc EHDP uptake. Our results suggest that regional bone blood flow is a major determinant of ^{99m}Tc EHDP uptake, but changes in regional tracer extraction efficiency are also important. This work increases our understanding of the basic mechanisms of ^{99m}Tc phosphate bone imaging. The results can be applied toward improved clinical interpretations, and benefit patients (soldiers) with trauma, bone grafts, osteomyelitis or other conditions which can be detected with these techniques.

PREFACE

We thank E. L. Barron, N. L. Fleming, M. E. Flynn, R. G. Hamilton, J. Jozsa and J. K. Warrenfeltz for their technical assistance.

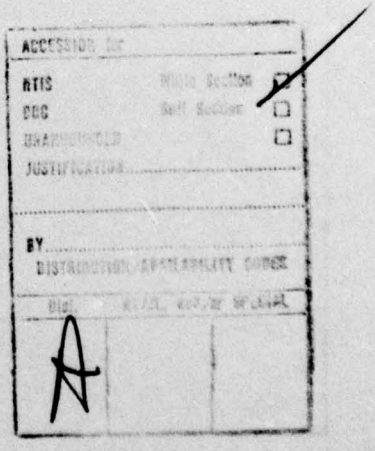

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FIGURE

TABLE

INTRODUCTION

The regional distribution of bone-seeking radiopharmaceuticals in the skeleton is potentially dependent on a number of factors including local alterations in blood flow, metabolic activity, osteogenesis, surface area for tracer exchange, capillary permeability, and the volume of interstitial fluid.[1,8] Several investigators have suggested that increased local blood flow is the major physiologic determinant of increased tracer deposition in skeletal lesions,[7,10,13,14] but this viewpoint has been challenged.[4,9] The present study was undertaken to evaluate the relationship between the skeletal uptake of ^{99m}Tc diphosphonate (ethane-1-hydroxy-1,1-diphosphonate (EHDP)) and relative bone blood flow measured with labeled microspheres under conditions of normal, decreased, and increased regional blood flow.

METHODS

Male Hla:(SD) rats weighing 400-700 g were used. The control group contained 17 animals. In another group (n = 12), the right femoral artery was ligated just distal to the inguinal ligament 24 hours prior to the tracer distribution study. In 39 rats the right tibia was fractured as described by Wray and Lynch[15] and the tracer study was performed 3 weeks later. In another 21 rats with 3-week-old right tibial fractures the right femoral artery was ligated 24 hours prior to the tracer study.

Each rat was injected by tail vein with ^{99m}Tc EHDP (0.1 ml containing 0.1 mg EHDP and 15 μCi ^{99m}Tc). Three hours later the rats were anesthetized with halothane and the skin, pectoralis muscle, and rectus abdominis muscle overlying the precordium were reflected. Using a 25-gauge butterfly infusion needle filled with heparinized saline, the left ventricle was punctured through the fourth intercostal space and an injection was made over 10-15 sec of 600,000-900,000 carbonized microspheres (15 $\pm$ 5 μm diameter; labeled with ^{85}Sr; suspended in 0.2-0.3 ml 10 percent dextran). Approximately 1 minute later, the rat was euthanatized and both tibiae were removed, carefully

dissected free of soft tissue, and weighed. The whole bones were counted in a NaI(Tl) crystal well counter; the counts in the ^{99m}Tc channel were corrected for the Compton scatter contribution from ^{85}Sr. The results in each animal for each tracer were expressed as an R-L ratio ((counts/g right tibia)/(counts/g left tibia)).

RESULTS

The R-L ratios for both ^{85}Sr microspheres and ^{99m}Tc EHDP in control animals were close to 1.0, as expected (Table 1). In the rats with right femoral artery ligation, the mean R-L ratios for both tracers were significantly less than the corresponding control values. The diphosphonate R-L ratio was higher than that obtained with microspheres in these animals. Both ratios were significantly higher than control values in animals with healing right tibial fractures. In this group the microsphere R-L ratio was greater than the diphosphonate ratio. However, on inspection of the individual results it was noted that

Table 1. Tibial R-L Ratios

Group	n	^{85}Sr-Microspheres	^{99m}Tc-EHDP
Control	17	0.94 ± 0.14	1.00 ± 0.05
Arterial Ligation	12	0.44 ± 0.17*	0.67 ± 0.14*†
Fracture	39	2.10 ± 0.87*	1.60 ± 0.34*†
^{85}Sr R-L ratio <1.7	18	1.37 ± 0.22*	1.38 ± 0.13*
^{85}Sr R-L ratio >1.7	21	2.72 ± 0.70*	1.78 ± 0.36*†
Fracture + Ligation	21	0.86 ± 0.32	1.29 ± 0.20*†

Results presented as mean ± 1 standard deviation

* Significantly different by unpaired t-test compared to control value at P<0.0001.

† Significantly different by paired t-test compared to corresponding microsphere value at P<0.001.

the two ratios corresponded quite closely when the microsphere R-L ratio was less than 1.7. At higher relative flow ratios (>1.7), the microsphere ratios were generally greater than the diphosphonate ratios. Therefore in Table 1, the results in the fracture animals have also been divided into two subgroups based on the observed value of the microsphere ratio (i.e., below or above 1.7).

Figure 1 shows the relationship between the microsphere and diphosphonate R-L ratios in the control, ligated, and fracture animals. The overall linear correlation for these 68 paired observations was highly significant ($r = 0.804$; $P<0.0001$). As noted above, the two ratios appeared to be linearly related in animals with microsphere R-L ratios less than 1.7. In these animals ($n = 47$), the linear correlation coefficient was 0.917 ($P<0.0001$). In animals with microsphere R-L ratios beyond this point the diphosphonate R-L ratio showed little further increase.

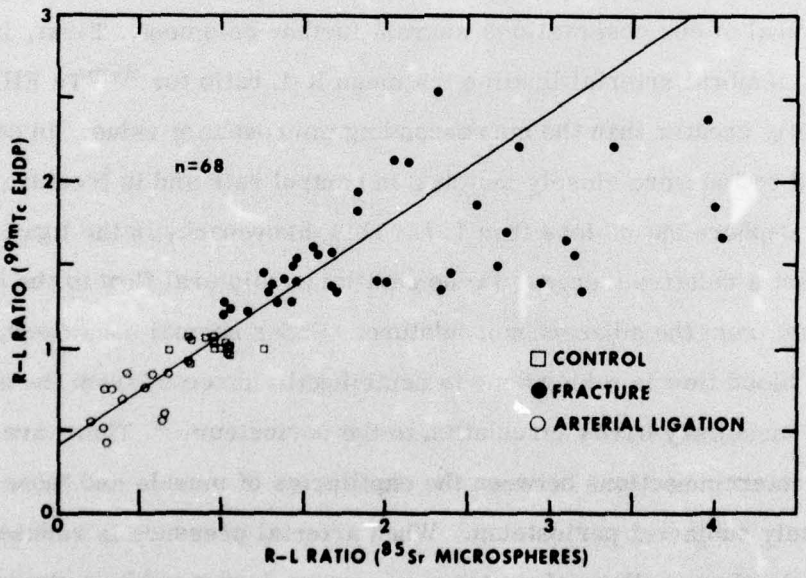

Figure 1. Relationship between tibial R-L ratios for ^{99m}Tc EHDP and ^{85}Sr microspheres. Each point represents the results for a single animal. The line shown is the calculated regression line based on the results of the 47 animals in which the ^{85}Sr microspheres R-L ratio was less than 1.7 (see text for explanation).

Arterial ligation in rats with healing tibial fractures resulted in a significant decrease in both ratios ($P < 0.0001$) compared to the values in the fracture group (Table 1). The diphosphonate R-L ratio was significantly greater than the microsphere ratio in these animals, a finding similar to that in the rats with only arterial ligation.

DISCUSSION

Our results demonstrate that the local, short-term deposition of ^{99m}Tc EHDP in the rat tibia is highly correlated with the distribution of bone blood flow. A decrease in relative tibial blood flow secondary to femoral arterial ligation is accompanied by a decrease in the relative uptake of ^{99m}Tc EHDP. Increased ^{99m}Tc EHDP uptake is noted in healing tibial fractures with moderately increased relative blood flow. Furthermore, femoral artery ligation on the side of a healing fracture results in significant diminution of both relative flow and ^{99m}Tc EHDP accumulation.

Several of our observations warrant further comment. First, in rats with unilateral femoral arterial ligation the mean R-L ratio for ^{99m}Tc EHDP was significantly greater than the corresponding microsphere value. In contrast, the paired ratios were closely matched in control rats and in fracture animals with microsphere ratios less than 1.7. This discrepancy in the ligation group may reflect a relative increase in the capillary collateral flow to the tibial periosteum from the adjacent musculature. Under normal conditions, the predominant blood flow in a long bone is centrifugally directed from the higher pressure medullary cavity circulation to the periosteum.[3] There are, however, abundant interconnections between the capillaries of muscle and those of the immediately subjacent periosteum. When arterial pressure is reduced in the entire limb, these collateral routes may assume increased hemodynamic significance. This would result in relatively greater delivery of ^{99m}Tc EHDP to bone as compared to labeled microspheres which would be trapped in the afferent arteriolar and capillary collaterals. An alternate explanation may be found

in the nonuniform long bone perfusion model proposed by Bosch.[2] According to this hypothesis, the tibia contains both "nutrient vessels" capable of substantial tracer exchange with bone mineral and "nonnutrient vessels" which allow no, or very limited, exchange. Under conditions of low flow, the relative proportion of nutrient vessels perfused is greater and the apparent extraction efficiency of ^{99m}Tc EHDP is increased compared to the control value.

Second, there was a similar discrepancy between the relative flow and ^{99m}Tc EHDP uptake in the animals with healing fractures subjected to arterial ligation. The same mechanisms proposed above could account for these findings. If, in addition, there was a local increase in the ^{99m}Tc EHDP extraction efficacy at the fracture site,[6] this would further magnify the effect of a flow reduction in predominantly nonnutrient vessels.

Third, we have observed that the diphosphonate R-L ratio increases more slowly than flow at high relative flows (microsphere R-L ratio >1.7). The most likely explanation for this finding is that the extraction efficiency for ^{99m}Tc EHDP *decreases* at high flow rates. This phenomenon has been noted by other investigators,[2,5] although the underlying mechanism remains open to question.

Our findings are largely in agreement with those of Genant et al.[7] These investigators demonstrated comparable changes in the relative blood flow and the uptake of several bone-seeking radiopharmaceuticals in the knees of rats in which one hind limb had been cooled and the other heated. Paradis and Kelly[10] have also recently demonstrated a close correspondence of blood flow and ^{85}Sr uptake in canine tibial fractures of varying ages.

In summary, our study suggests that bone blood flow is a major physiologic determinant of the regional skeletal uptake of ^{99m}Tc EHDP. Increased skeletal blood flow is found in a large variety of disorders which are associated with abnormal bone images.[1,12] However, pathophysiologic alterations in the regional extraction efficiency for ^{99m}Tc EHDP also appear to be important and may predominate at high regional flow rates. Changes in extraction efficiency could be mediated by several mechanisms including preferential binding of

^{99m}Tc phosphate complexes to immature collagen,[9,11] the association of increased new bone formation with increased surface area for tracer exchange,[1,8] and changes in capillary permeability.[6] An assessment of the relative importance (and, perhaps, interdependence) of bone blood flow and these other factors will require further study.

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